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Clinical Immunology Review Series: An approach to the patient with recurrent infections in childhood

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Summary

Recurrent or persistent infection is the major manifestation of primary immunodeficiency, which also results in atypical infection with opportunistic organisms. Young children are also vulnerable to infection and recurrent infection is common. While most children with recurrent infection have a normal immunity, it is important to recognize the child with an underlying primary immunodeficiency and investigate and treat appropriately and yet not over investigate normal children. Prompt, accurate diagnosis directs the most appropriate treatment, and early and judicious use of prophylactic antibiotics and replacement immunoglobulin can prevent significant end organ damage and improve long-term outlook and quality of life. This paper describes important presenting features of primary immunodeficiency and indicates when further investigation is warranted.

Keywords: antibody deficiency, chronic granulomatous disease, primary immunodeficiency, recurrent infection, severe combined immunodeficiency

Introduction

In infancy and early childhood the immune system encounters antigens for the first time, mounting immune responses and acquiring memory. Young children mix with other children in families or nursery and are exposed to many pathogens. Young children are therefore vulnerable to infection and recurrent infection is common. A pattern of recurrent or persistent infection is the major manifestation of primary immunodeficiency (PID). PID also results in atypical infection with opportunistic organisms. While most children with recurrent infection have a normal immune system, it is important to recognize the child with an underlying PID and investigate and treat appropriately, and yet not over-investigate normal children. Prompt, accurate diagnosis of PID helps to direct the most appropriate treatment, predict prognosis and facilitate genetic counselling for the family. An increasing number of PID diseases are now recognized [1,2], and effective treatments are possible. Early and judicious use of prophylactic antibiotics and replacement immunoglobulin can prevent significant end organ damage and improve long-term outlook and quality of life and new, easier-to-use formulations are emerging [3,4]. Haematopoietic stem cell transplantation is used for an increasing number of severe immunodeficiencies and in centres specializing in treating these conditions survival and cure of the disease can reach up to 95%, depending on the condition of the patient at time of treatment and the donor available [5]. Risk factors of haematopoietic stem cell transplantation include end organ damage of liver and lungs and corresponding increase in significant post-transplant complications and reduction in survival. Because of significant advances in treatment it is important to recognize children with PID early before significant end organ damage has occurred to maximize the opportunity for successful treatment and normal lifespan.

This paper will outline important presenting features of PID and indicate in which children further investigation is warranted. Knowledge of normal immunity and specific warning signs and symptoms can help to distinguish those children with underlying PID from those who are normal.

Physiological immunodeficiency of immaturity

Infants exhibit physiological immaturity of the immune system, more marked in the preterm or sick infant [6]. Neutrophil bone marrow reserves are easily exhausted and neutrophil counts often fall in the face of sepsis. Chemotaxis is reduced, as are complement levels and function.

Circulating mature T and B lymphocytes are present in the fetus from the second trimester and lymphocyte numbers rise with gestation. However, lymphocyte responses to antigens, particularly immunoglobulin production, are limited until birth. Naive neonatal T lymphocytes are more difficult to stimulate than those of adults. Diminished T lymphocyte CD40 ligand expression reduces signalling to B lymphocytes through the CD40 receptor and depresses immunoglobulin isotype switching. Maternal immunoglobulin G (IgG) is transferred to the fetus during the third trimester via the placenta, and so makes up for the deficit of intrinsic IgG production in the neonate. This is compromised with preterm birth and premature infants have significantly reduced IgG levels. The protective effect of maternal immunoglobulin depends on the mother having appropriate antigen-specific IgG antibody. Neonatal T lymphocyte responses are directed towards a T helper 2 (Th2) [interleukin (IL)-4, IL-5, IL-10] rather than a Th1 (IL-2, interferon-γ, tumour necrosis factor-α) response which may contribute to susceptibility to intracellular bacterial pathogens such as listeria monocytogenes or salmonella species. The immune response matures quite rapidly after birth. Initially IgM is produced, but as maternal IgG decays intrinsic IgG responses develop. By 2 months of age infants can produce IgG antibody responses to protein and conjugate vaccine antigens. As the maternal IgG level decays there is a physiological nadir in IgG level between 3 and 6 months, which may be prolonged while the infant's production is developing. Serum IgA levels rise more slowly than the other classes of immunoglobulin, not reaching adult levels until late adolescence. Production of IgG2 subclass antibody in which most anti-polysaccharide antibody responses are found is delayed in young children, partly explaining infant susceptibility to polysaccharide encapsulated organisms such as pneumococcus [7,8]. These responses normally mature between about 2–5 years of age, but may be delayed beyond this.

Features suggestive of PID

Careful history and examination will indicate whether an underlying PID is likely to be causing the presenting symptoms of recurrent infection. The age at presentation and pattern of infection will often indicate in which part of the immune system the defect may reside, and so which investigations are appropriate (Table 1).

Table 1. Clues to the presence of primary immunodeficiency.

Age at presentation		
	Neonatal period	Omenn syndrome
		Severe congenital neutropenia
		DiGeorge syndrome
		LAD
		Reticular dysgenesis
	<6/12	SCID
		Other T cell immunodeficiency
		CD40 ligand deficiency
	6/12–5 years	Wiskott–Aldrich syndrome
		DiGeorge syndrome
		Chronic mucocutaneous candidiasis
		Hypogammaglobulinaemia
		Phagocytic defect – CGD
	>5 years	Late presentation of above
		AT, other DNA repair disorder
		Common variable immunodeficiency
		Specific antibody deficiency
		Complement disorder

AT, ataxia telangeictasia; CGD, chronic granulomatous disease; LAD, leucocyte adhesion deficiency; SCID, severe combined immune deficiency.

Age

Neonatal period. Delayed separation of the umbilical cord beyond 2 weeks is characteristic of leucocyte adhesion deficiency type I (LAD), but may also be seen in patients with IL-1 receptor-associated kinase-4 (IRAK4) deficiency or neutropenia [9]. In patients with LAD, erosive perianal ulcers may also be present because of obstruction of small vessels with neutrophils that are unable to egress through the vessel walls to the site of infection. Omphalitis is also suggestive of a neutrophil disorder such as LAD, severe congenital neutropenia (SCN) or chronic granulomatous disease (CGD).

A number of other co-existent features to infection may present in the neonatal period and suggest an underlying PID. Erythroderma presenting in infancy with associated massive lymphadenopathy and hepatosplenomegaly is highly suggestive of Omenn syndrome, an atypical variant of severe combined immunodeficiency (SCID). Histological findings resemble graft-*versus*-host disease, because of a few expanded clones of aberrant autoreactive autologous T lymphocytes.

Cardiac defects associated with hypocalcaemia and facial dysmorphism suggest DiGeorge syndrome or CHARGE (coloboma, heart disease, atresia of the choanae, retarded growth and mental development, genital abnormalities and ear malformations and hearing loss) association, because of defects in the CHD7 gene. In both these conditions thymic aplasia is rare but causes a severe T lymphocyte immunodeficiency. A rare form of SCID, reticular dysgenesis, usually presents in the neonatal period with cytopenia which may affect platelets, neutrophils and erythrocytes.

Less than 6 months. Severe phagocytic defects, such as SCN or LAD, usually present within the first few days or weeks of life. Presentation within the first few months of life is highly suggestive of a significant T lymphocyte or combined immunodeficiency, such as SCID or CD40 ligand deficiency. Atypical forms of disease usually present later and may present with additional features to infection including autoimmunity.

Six months to 5 years. Defects in antibody or complement are more likely to present at this age [10], although late presentation of combined immunodeficiency is also possible. Presentation of antibody deficiency occurs beyond 4–6 months once the placentally acquired maternal IgG has decayed [11,12]. Defects in neutrophil function, such as CGD, may present in infancy, although the diagnosis is often made later [13]. Immunodeficiency associated with DNA repair defects such as ataxia telangiectasia or Nijmegen breakage syndrome present commonly with gait abnormalities or neurodevelopmental delay [14], and usually present to the neurologist or developmental paediatrician rather than immunologist.

Greater than 5 years. In children over the age of 5 years common variable immunodeficiency, a specific antibody deficiency or disorders of the complement system are more likely [15,16].

Organ-specific manifestations

Presentation in particular organ systems can give an indication of a specific underlying immunodeficiency.

Respiratory infection. The lung is a major interface with the environment; pulmonary infection therefore is a frequent consequence of PID, although it is also common in immunocompetent individuals. Many children who present with recurrent respiratory infection are investigated for cystic fibrosis, but the suspicion of an underlying cause for recurrent respiratory infection should also prompt investigation for PID. Children presenting in early infancy with persistent or recurrent bronchiolitis should be considered to have SCID. Prolonged interstitial pneumonia because of either viral infection such as parainfluenza virus or cytomegalovirus or *Pneumocystis jerovici* is suggestive of human immunodeficiency virus (HIV) infection, SCID, CD40 ligand deficiency or other combined immunodeficiency [17,18]. Interstitial pneumonia with no obvious infective cause should prompt strenuous efforts to find an infecting organism, and bronchoalveolar lavage or lung biopsy may be necessary [19]. The finding of *Pneumocystis jerovici* should always suggest an underlying immunodeficiency [20–22].

Recurrent sinobacterial infection, particularly occurring after 6 months of age, is more suggestive of a humoral immunodeficiency. The most common cause is transient hypogammaglobulinaemia of infancy, because of a prolonged physiological nadir of IgG, but this is always a retrospective diagnosis following resolution of hypogammaglobulinaemia [23]. The finding of low IgM as well as IgG makes this diagnosis less likely [24,25], as does an absence of vaccine antigen responses, and other causes of hypo- or agammaglobulinaemia, such as X-linked or autosomal recessive agammaglobulinaemia should be considered [26].

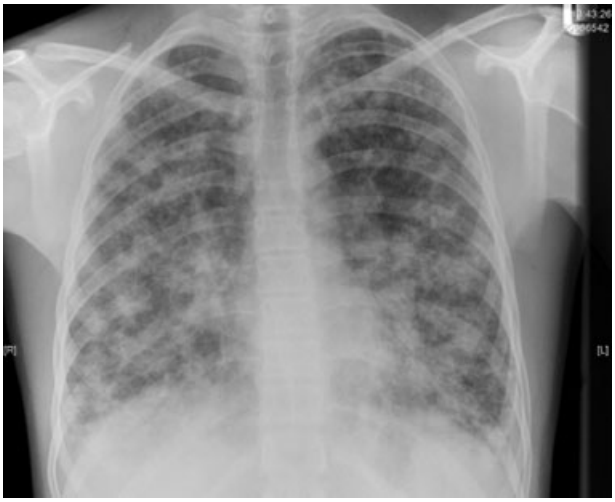

Fig. 1. Chest radiograph of a 15-year-old boy with autosomal recessive chronic granulomatous disease, showing bilateral dense infiltrates because of *Aspergillus fumigatus* and *Absidia corymbifera* pneumonitis (courtesy of the Paediatric Immunology Unit, Newcastle General Hospital).

Specific antibody deficiency, particularly to polysaccharide organisms, is difficult to diagnose before 5 years of age, as normal infants are unable to produce polysaccharide-specific IgG. Other causes of pneumococcal antibody deficiency include atypical X-linked agammaglobulinaemia [27] and defects in the Toll-like receptor signalling pathway, such as defects in nuclear factor kappa B (NFκB) essential modulator (NEMO) and IRAK4 [28].

The finding of staphylococcal lung infection leading to pneumatocele formation, particularly when associated with eczema, should raise the suspicion of the hyper-IgE syndrome [29,30]. Fungal pneumonias are uncommon and CGD should be considered [13], particularly in the case of fulminant pneumonitis [31] (Fig. 1). Common variable immunodeficiency is uncommon in children, but may present with recurrent sinopulmonary infection later in childhood [32]. Complement deficiency may present with sinopulmonary infection later in childhood. Children with neutrophil defects such as cyclical neutropenia or CGD may also present with recurrent respiratory infection.

Gastrointestinal presentations. Failure to thrive and malabsorption associated with infection-related diarrhoea are seen

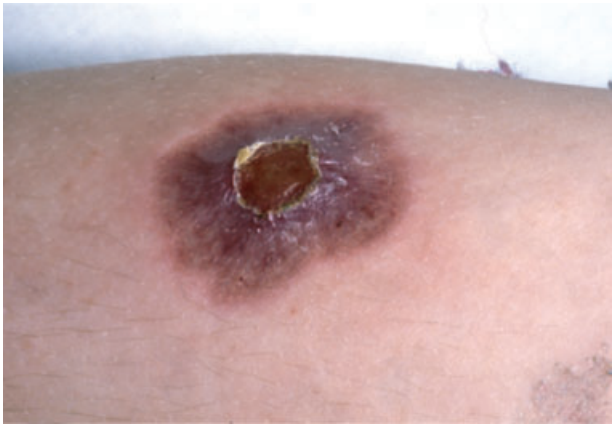

Fig. 2. Pyoderma because of *Pseudomonas auruginosa* infection in a boy with X-linked agammaglobulinaemia (courtesy of the Paediatric Immunology Unit, Newcastle General Hospital).

commonly in T cell immunodeficiencies such as SCID or HIV infection. Infection is often persistent with failure to clear virus and there may be an associated malnutrition because of malabsorption. Persistent non-infective diarrhoea in boys who require parental nutrition, with associated eczema and recurrent respiratory infection, should raise the suspicion of immunodysregulation, polyendocrinopathy, enteropathy or X-linked (IPEX) syndrome [33].

Hepatic abscesses or other abscesses because of *Staphylococcus aureus* or fungal infection are characteristic of CGD [13]. These patients also present rarely with pyloric obstruction and vomiting but more commonly with bloody diarrhoea and a colitis that clinically and histologically may resemble Crohn's disease, with granulomata present on a gut biopsy [34]. Schwachman–Diamond syndrome should be excluded in patients presenting with exocrine pancreatic insufficiency associated with neutropenia. Persistent or prolonged enteritis because of *Cryptosporidium parvum* suggests a T lymphocyte immunodeficiency [35]. Sclerosing cholangitis in an older boy is suggestive of infection with *Cryptosporidium parvum* associated with CD40 ligand deficiency.

Dermatological presentations. Dermatological presentations of PID are common. In a boy with recurrent sinopulmonary infection with associated eczema and petechiae, Wiskott–Aldrich syndrome is likely. Eczema in association with staphylococcal pneumatoceles is suggestive of hyper-IgE syndrome and an eczematous rash associated with thoracic or abdominal abscesses suggests CGD. Perianal ulceration, particularly in the newborn period, is associated with a high neutrophil count but a lack of pus is indicative of LAD. Pyoderma may be a feature of antibody deficiency [36] (Fig. 2). Persistent mucosal candida infection may be suggestive of SCID, chronic mucocutaneous candidiasis or hyper-IgE syndrome. Mucocutaneous albinism may be associated with disorders of cell-mediated killing, such as Griscelli syndrome or Chediak–Higashi syndrome [37]. Midline ulceration may be seen in major histocaompatibility complex class I deficiency, although ulceration in other areas may also be seen [38]. Systemic lupus erythematosus (SLE) is a feature of deficiencies of the complement proteins and may also be seen in carriers of X-linked CGD. Telangiectasia or photosensitivity with recurrent infection are suggestive of a DNA repair disorder such as ataxia telangiectasia [14] (Fig. 3).

Neurological features. Neurodevelopmental delay may be associated with PID. Spastic diplegia with dysarthria is a common presenting feature of purine nucleotide phosphorylase-deficient SCID. Unsteady gait associated with late walking is suggestive of ataxia telangiectasia; the telangiectasia usually present first on the conjunctival bulbar, although often not until 3 or 4 years of age. Developmental delay with typical facial features may be seen in patients with DiGeorge syndrome or with the immunodeficiency centromeric instability facial dysmorphism syndrome. Speech delay is a common presentation of DiGeorge syndrome. Microcephaly and associated developmental delay is suggestive of a DNA repair disorder such as Nijmegen breakage syndrome or DNA ligase 4 deficiency. Neurological deterioration is a late feature of Chediak–Higashi syndrome. Enteroviral meningo-encephalitis should raise the suspicion of humoral immune deficiency, particularly X-linked agammaglobulinaemia.

Haematological presentations. A full blood count is one of the most frequent investigations, and careful examination of the result may yield useful information that is often overlooked. Most patients with SCID are lymphopenic, but this is often missed on initial presentation [39]. Lymphocyte counts are higher in infancy than in adults and an absolute lymphocyte count of $< 2{\cdot}8 \times 10^9$/l is two standard deviations below the mean until 1 year of age. The finding of lymphopenia in a child with recurrent or persistent infection should prompt reinvestigation: lymphopenia present on two

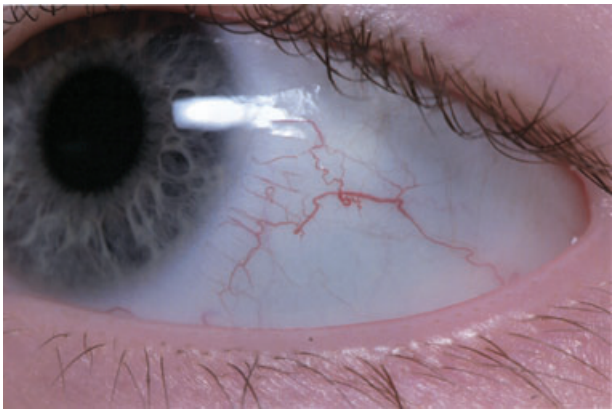

Fig. 3. Bulbar telangiectasia on the conjunctivae of a girl with ataxia telangiectasia (courtesy of the Paediatric Immunology Unit, Newcastle General Hospital).

or more occasions, particularly in an infant, is highly suggestive of SCID and warrants further investigation. However, a normal lymphocyte count does not preclude the diagnosis of SCID.

Erythrophagocytosis may be a presenting feature of a number of primary immunodeficiencies, in particular X-linked lymphoproliferative disease (XLP) [often associated with Epstein–Barr virus (EBV) infection], Chediak–Higashi syndrome, Griscelli syndrome and familial haemophagocytic lymphohistiocytic syndromes [40,41]. Recurrent episodes of erythrophagocytosis are highly suggestive of an underlying PID.

Neutropenia may be found in a number of PIDs [42]. Neutropenia occurring every 3–4 weeks, often with an associated fever, infection or mouth ulcers, is suggestive of cyclical neutropenia. Some cases are associated with elastase 2 gene defects also found in SCN. These patients present with bacterial sepsis, skin abscesses or cellulitis, mucosal infections (gingivitis, stomatitis, apthous ulcers, periodontitis) and respiratory infection [43]. Other causes of SCN include HCLS1-associated protein X-1 deficiency [44] and Wiskott-Aldrich syndrome protein deficiency, where the defect causes continuous activation of the gene [45]. Neutropenia may also be found in CD40 ligand deficiency and X-linked agammaglobulinaemia [12,17].

Autoimmune cytopenia can indicate PID. Wiskott–Aldrich syndrome should be excluded in boys with thrombocytopenia – a small mean platelet volume (< 5fl) is pathognomic. Patients with DiGeorge syndrome may present with autoimmune cytopenia or other autoimmune features. Human herpes virus infection is associated with cytopenias in patients with autoimmune lymphoproliferative syndrome, who often present with lymphadenopathy and hepatosplenomegaly. Autoimmune cytopenia is also a feature of IPEX syndrome, with associated autoimmune enteropathy and recurrent infection.

The finding of myelodysplasia should raise the suspicion of XLP, or a DNA repair defect such as Nijmegen breakage syndrome.

Skeletal and connective tissue features. Bony abnormalities may be a feature of underlying PID. Characteristic abnormalities in adenosine deaminase-deficient SCID include cupping at the end of the ribs demonstrated on a chest radiograph. Patients with Schwachman–Diamond syndrome also have variable skeletal abnormalities including rib cage abnormalities and metaphyseal dysostosis. Other well-recognized bony abnormalities associated with immunodeficiency include cartilage hair hypoplasia which presents with a short-limbed dwarfism. The immunodeficiency in these patients is variable; some have humoral immunodeficiency while others have features more consistent with T lymphocyte immunodeficiency. Hyper-extensibility and hypodense bones are a feature of hyper-IgE syndrome. Such patients may describe pathological fractures and delayed primary dental deciduation [30]. Patients with defects in NEMO may present with osteopetrosis [46].

Table 2. Examples of association between infecting organisms and most likely type of immune defect.

Organism	Candidate immune defect
Pneumococcus, *Haemophilus influenzae*	Antibody, complement
Staphylococcus	Neutrophil
Meningococcus	Complement
Gram-negative bacteria	Neutrophil
Salmonella	Type 1 cytokine defects, cell-mediated
Cryptosporidium	Cell-mediated
Giardia lamblia	Antibody, cell-mediated*
Mycoplasma spp.	Antibody
Candida albicans	Cell-mediated, neutrophil, monocyte
Aspergillus spp.	Neutrophil
Herpes viruses (e.g. CMV)	Cell-mediated
Enteroviruses	Antibody, cell-mediated
Other viruses (e.g. measles)	Cell-mediated
Mycobacteria (typical and atypical)	Type 1 cytokine defects (genes (IFN-γR1, IFN-γR2, STAT1, IL-12RB1 and IL-12B), NFκB signalling pathway defects (NEMO)
Bacille Calmette–Guérin (BCG)	Cell-mediated, type 1 cytokine defects

*Particularly patients with HIV. CMV, cytomegalovirus; IFN, interferon; IL, interleukin; NFκB, nuclear factor kappa B; NEMO, NFκB essential modulator; STAT1, signal transducer and activator of transcription 1.

Lymphoreticular features. Malignancy is more common in PID and may arise in any of the immunodeficiencies [2]. EBV-associated lymphomas are particularly described in XLP and Wiskott–Aldrich syndrome. Lymphoid malignancies are also more common in DNA repair defects such as ataxia telangiectasia and Nijmegen breakage syndrome. Non-Hodgkin's lymphoma is described in autoimmune lymphoproliferative syndrome, although in some of these patients the diagnosis may be a mistaken for clonally expanded, non-malignant, T lymphocyte populations [47]. Lymphoreticular malignancy is described in common variable immunodeficiency [48]. Hepatoma is a well-recognized complication of CD40 ligand deficiency, associated with cryptosporidial infection.

Infecting organism

While it is rarely possible to predict a specific PID on the basis of infection with a particular microbe, certain infections warrant careful consideration of possible underlying PID (Table 2). *Pneumocystis jerovici* pneumonitis should always prompt a search for an underlying cause, such as HIV infection, or a T lymphocyte immunodeficiency. Invasive *S.*

aureus infection or *Burkholderia cepacia* septicaemia is associated with CGD, as are aspergillus or other fungal abscesses. An aspergilloma in a pneumatocoele is suggestive of hyper-IgE syndrome. Human herpes virus infections are common in WAS, and EBV-associated lymphoma is suggestive of WAS or XLP. Disseminated atypical mycobacterial infection is suggestive of a Th1 cytokine defect, as is disseminated BCG infection, which may also be found in SCID. Infection with environmental mycobacteria is also a feature of defects in the NFκB signalling pathway. Recurrent meningococcal infection suggests a defect in one of the terminal components of complement. Sinopulmonary infection with *S. pneumoniae* or *Haemophilus influenzae* is found in antibody or complement deficiency. Invasive pneumococcal disease is suggestive of defects in the NFκB signalling pathway, particularly if there is no associated fever or inflammation. Severe enteroviral infection suggests agammaglobulinaemia. Herpes simplex encephalitis suggests a defect in Toll-like receptor 3 or UNC-93B. This list is not exhaustive, and it is possible for the conditions mentioned to present with infection because of other organisms.

Family history

Careful evaluation of the family history can be helpful in determining the likelihood of PID. Consanguinity is suggestive of autosomal recessive disease. Several PID are X-linked; a history of male infection or unexplained infective deaths in infancy or early childhood on the maternal side of the family is significant. A history of lymphoma in male relatives would suggest XLP or Wiskott–Aldrich syndrome. *P. jerovici* pneumonia presenting in the neonatal period may suggest X-linked SCID or CD40 ligand deficiency. Death from infection in infancy is highly suggestive of SCID and should be taken seriously, even in families where there is no consanguinity. A history of lymph node abscesses associated with granulomas that were tuberculosis-negative or a history of colitis is suggestive of CGD and a history of SLE in related females is strongly suggestive of this diagnosis. Autoimmune disease, if associated with candida, suggests chronic mucocutaneous candidiasis. A history of severe neonatal diarrhoea requiring total parenteral nutrition, possibly associated with diabetes, is highly suggested of IPEX syndrome. It becomes more difficult when the history stretches back three or four generations in deciding whether infant deaths are significant or may reflect higher infant mortality rate at that time. However, a history of childhood infective deaths should not be dismissed lightly.

Who to investigate

This is a difficult question to answer, as infection in childhood is very common. Until effective screening programmes are in place [49], a high index of clinical suspicion is needed. Compared with other children, an immunodeficient child is likely to have more infections that take longer to resolve or have an atypical course. Infections with common organisms may run an unusually severe course, e.g. haemorrhagic chickenpox, or fail to respond to standard treatments, e.g. bacterial pneumonia which fails to respond to appropriate antibiotic therapy. It is considered generally that a child who has suffered two invasive infections or one invasive and many minor infections should be investigated. Other presenting features provide a useful guide (Table 3). However, the infection should be taken in context with other findings in the history and examination and the family history. When evaluating the number of infections, other factors such as parental smoking, attendance at nursery and anatomical problems should be considered. A useful diagnostic algorithm has been published recently which will be useful for specialists and non-specialists alike [50,51], but the critical message is to consider the diagnosis of immunodeficiency.

Table 3. Specific warning signs of primary immunodeficiency.

- Eight or more new infections within 12 months
- Two or more serious sinus infections or episodes of pneumonia within 1 year
- Two or more months on antibiotics with little effect
- Failure of an infant to gain weight or grow normally
- Recurrent deep skin or organ abscesses
- Persistent superficial candidiasis after age 1 year
  - Episode of opportunistic infection
  - Complication associated with live vacination
- Need for intravenous antibiotics to clear infections
- Two or more invasive infections
- A family history of primary immune deficiency
- Unexplained autoimmune disease

How to investigate

With an ever-increasing repertoire of immunological investigations, choosing which investigations to perform can be perplexing. Routine screening of newborn infants for SCID by use of an air-dried blood spot on filter paper is not yet available, but pilot studies are being planned [52]. Use of the diagnostic algorithm [50] will aid choice of appropriate investigations. The most useful first-line immunological investigations include a full blood count with a differential count on the leucocytes, and lymphocyte subset analysis looking at numbers (not simply percentages) of $CD3^+$, $CD4^+$, $CD8^+$, human leucocyte antigen D-related$^+$ T lymphocytes, B lymphocytes ($CD19^+$, $CD20^+$) and natural killer (NK) cells ($CD16^+$, $CD56^+$). Serum immunoglobulins should also be measured, including IgM, IgA, IgG, IgG subclasses and responses to vaccinations (tetanus and *Haemophilus influenzae* B, pneumococcus), taken 4 weeks after vaccination if not previously exposed to vaccine antigen. Care should be taken when measuring pneumococcal responses – many children will have received the conjugate pneumococcal vaccine, and so serotype-specific responses should be measured.

These investigations will help to diagnose many severe immunodeficiencies, but further investigations may be needed, including the measurement of lymphoctye proliferation after stimulation with specific antigen or mitogen, the measurement of cell surface markers such as CD40 ligand, more detailed investigation of lymphocyte phenotype including measurement of recent thymic emigrants, lymphocyte receptor spectratyping and class-switched memory B lymphocytes. Other investigations, more usually in the research setting, are available and advice should be sought from an appropriate specialist. Genetic investigation is now also available for many disorders, which may have implications for other family members.

Finally, it has recently been suggested that any individual presenting with infection is immunodeficient [53]. There are certainly rare examples of single infections such as herpes simplex encephalitis being associated with genetic defects. Perhaps, therefore, the question to be asked in a child presenting with infection is not 'Who should be investigated for primary immunodeficiency?', but 'What are the reasons for not investigating this child further?'

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